REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on August 14, 2002. Claims 1-37 have been rejected. Claims 15-37 have been cancelled herein without prejudice. Claims 1-14 are pending.

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. Applicants reserve the right to prosecute the originally filed claims in the future. The comments in the Office action are now addressed in turn.

Rejections under 35 U.S.C. §103

Siciliano *et. al.* in view of Cronin *et. al.*

The Office action rejects Claims 1-6 and 12-14 under 35 U.S.C. §103(a) as being anticipated by Siciliano *et. al.* (U.S. Patent 5,538,869) in view of Cronin *et. al.* (U.S. Patent 6,309,823). Specifically, it is asserted that, in combination, Siciliano *et. al.* and Cronin *et. al.* describe the method of claims 1-6 and 12-14. *See* paragraph 1 at page 3 of the Office Action. The applicants must respectfully disagree, asserting that neither of the cited references, alone or in combination, teach the presently claimed methods.

As previously discussed in Applicant's Amendment A, Siciliano *et. al.* describe a method whereby primer sets are used to prepare DNA probes specific for a chromosome for use in painting individual chromosomes in metaphase cell spreads and interphase nuclei by the "inter-Alu-PCR" method. The methods describe two methods for enriching the probes for chromosome-specific non-repeat containing DNA sequences prior to application to cells. Both methods employ the addition and hybridization of repeat sequence-rich human DNA to the probe DNA to be enriched for non-repeat DNA.

In contrast, in the present invention no repeat sequence-rich DNA is added to the nucleic acid fragments that are to be enriched for non-repeat containing DNA. Rather, single stranded forms of the population of nucleic acid fragments are incubated under annealing conditions, whereby those having repeat sequences "preferentially hybridize *to*

each other relative to nucleic acid fragments lacking repeat sequences" [emphasis added]. Neither Siciliano *et. al.* nor Cronin *et. al.* teach the hybridization of single stranded forms of nucleic acid fragments having repeat sequences "to each other".

In addition, the present invention teaches the separating of single stranded forms of the population of nucleic acid fragments from annealed double stranded forms, the single stranded forms being enriched for nucleic acids lacking repeat sequences. Neither Siciliano *et al.* nor Cronin *et al.* teach this aspect of the present invention. Cronin *et al.* does not discuss this limitation at all, and the description by Siciliano *et al.* does not discuss the separation of single stranded from double stranded DNA as taught by the present invention.

Further, the description by Siciliano *et al.* is not enabling for what it does disclose. Specifically, Siciliano *et al.* describe a method to "completely remove repeat sequences" that involves amplifying terminal Alu sequences, combining these sequences with low-Cot DNA (which represents Alu and other repeat sequences), and covalently linking the Alu and low-Cot DNA sequences to diazobenzyloxymethyl cellulose (column 14, line 37 to column 15, line 8). Then the Alu and low-Cot DNA sequences are hybridized with the probes such that the subset of probes containing repeat sequences will hybridize to the sequences bound to the cellulose and may be centrifuged away. Hence, the method of Siciliano *et al.* as described in the reference would remove *all* the probe from the population since all the probe contains Alu repeats at the ends (column 14, lines 45-54).

Applicants respectfully maintain that this is not an enabling description since there would be no probe left for hybridization to the chromosome spread. Since there is no enablement of this limitation of the present invention, there can also be no teaching of this limitation in Siciliano *et al.* Therefore, not every claim limitation of the present invention is taught by the cited references as is required to establish a *prima facia* case of obviousness.

Applicants also submit that the Examiner must take the references as a whole into consideration (the critical inquiry is whether "'there is something in the prior art as a whole *to suggest* the desirability, and thus the obviousness, of making the combination.'" *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556, 225 USPQ 26 (Fed. Cir.

1985) (emphasis in the original), quoting *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)). Furthermore, "[i]t is impermissible, within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965), cited in *In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986). As such, the mere fact that the teachings of the references can be modified or combined does not establish a motivation or suggestion to combine and make the resultant combination *prima facia* obvious. The references must suggest the desirability of the combination.

The examiner argues that Cronin *et. al.* suggests the desirability of combination with Siciliano *et. al.*, but the Applicants must respectfully disagree. Specifically, Cronin *et. al.* does not suggest the need or desire to combine with a method for removing repeat sequences from a nucleic acid population, as is discussed by Siciliano *et. al.* On the contrary, Cronin *et. al.* discusses a method to use probe arrays *in combination with* repeat sequences. In this way, Cronin *et. al.*, in fact, *teaches away* from the reference of Siciliano *et. al.*

Further, a proposed modification or combination of references that would destroy the intended function of one or both of the references cannot establish *prima facia* obviousness. The method of Siciliano *et. al.* is intended to localize a nucleic acid population to a specific region on a specific chromosome, but when a probe array is used in place of a whole chromosome this intended function is not accomplished. In some instances, the genomic positions of the probes on the array may be known, but in many instances they are not known. For example, if a probe array is created based solely on expression in a particular tissue, no information is known about the positions of the probes in the genome. In addition, if the genome has undergone rearrangements, such as insertions, deletions, translocations, and the like, any information regarding where the probes normally lie in the genome is irrelevant.

In sum, the Applicants submit that the claims are unobvious over Siciliano *et. al.* and Cronin *et. al.*, taken either alone or in combination. Thus, the Applicants respectfully

assert that the Examiner has not established a *prima facie* case of obviousness, and request that this rejection be withdrawn.

Siciliano *et al.* in view of Cronin *et al.* further in view of Arnold *et al.*

The Office action rejects Claims 1-14 under 35 U.S.C. §103(a) as being anticipated by Siciliano *et. al.* (U.S. Patent 5,538,869) in view of Cronin *et. al.* (U.S. Patent 6,309,823) further in view of Arnold *et al.* (U.S. Patent 5,714,354). Specifically, it is asserted that while, in combination, Siciliano *et. al.* and Cronin *et. al.* describe the method of claims 1-6 and 12-14, Arnold *et. al.* discuss the separation of nucleic acid fragments by successively performing hydroxyapatite chromatography and HPLC. *See* paragraph 1 at page 11 of the Office Action. The Applicants must respectfully disagree, asserting that none of the cited references, alone or in combination, teach the presently claimed methods.

As discussed above, neither Siciliano *et. al.* nor Cronin *et al.* teach the hybridization of single stranded forms of nucleic acid fragments having repeat sequences "to each other". In addition, the Arnold *et. al.* reference describes methods to purify a polysaccharide using HPLC to remove "nucleic acid contaminants". There is no teaching in Arnold *et. al.* of hybridization of single stranded nucleic acids to each other. Thus, there is no teaching in any of these cited references of the invention claimed herein, even if the references are combined.

Further, as discussed in Amendment A, the Examiner argues that Arnold *et. al.* describe a method of separating nucleic acid fragments by successively performing hydroxyapatite chromatography and HPLC. As cited by the Examiner, "The final purification step utilizing hydroxyapatite yields a highly purified product as indicated by the HPLC chromatogram and corresponding UV absorbance readings". However, the "purified product" to which Arnold *et. al.* refer is a polysaccharide and not a nucleic acid.

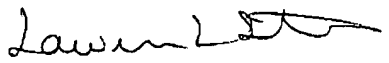
Although the invention of Arnold *et. al.* does use hydroxyapatite chromatography and HPLC to separate nucleic acids *from* a polysaccharide preparation, it does not teach the method of the present invention to use hydroxyapatite chromatography and HPLC to separate single stranded nucleic acids from annealed double stranded nucleic acids.

Thus, the combination of the references does not provide the teachings necessary to successfully obtain the presently claimed invention since all the elements of the claimed invention are not disclosed by either of the cited references, alone or in combination. Thus, the Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness, and request that the rejection be withdrawn.

Conclusion

For the reasons set forth above, the Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, please telephone the undersigned collect at 650-625-4555.

Respectfully submitted,



Lauren L. Stevens
Reg. No. 36,691

Perlegen Sciences
2021 Stierlin Court
Mountain View, CA 94043
Tel: (650) 625-4555
Fax: (650) 625-4574